

Attorney Docket No.: DRE-0067
Inventors: Laurencin et al.
Serial No.: 10/052,121
Filing Date: January 17, 2002
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REMARKS

Claims 1-3, 5 and 6 are pending in the instant application. Claims 1-3, 5 and 6 have been rejected. Claim 1 has been amended. Support for the amendment is provided in the specification at page 6, lines 27-34, page 8, line 31 through page 9, line 8, page 10, line 18 through page 11, line 21, page 12, line 1 through page 13, line 1 and page 15, lines 6-10. No new matter is added by this amendment. Reconsideration is respectfully requested in light of this amendment and the following remarks.

Rejection of Claims 1-3, 5 and 6 under 35 U.S.C. 103(a)

The rejection of claims 1-3, 5 and 6 as being unpatentable over Starling et al. (U.S. Patent 6,210,715) in view of Crotts et al. has been maintained. Arguments presented by Applicants in the last response were deemed unpersuasive as the Examiner suggests the rejection to be based on using the biodegradable polymer of Crotts et al. to produce the hollow microspheres of Starling et al. for producing an aggregate of hollow microspheres having a density of about 1.00 -1.12 gms/cc.

Applicants respectfully traverse this rejection.

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MPEP § 2143 states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. The cited combination does not meet these criteria.

MPEP 2143.01 and the case law are clear; the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In *re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Although a prior art device may be capable of being modified to run the way the apparatus is claimed, there must be some suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.

This required suggestion or motivation to replace the calcium phosphate based microspheres of Starling with the polymeric hollow microspheres of Crotts is not present in the cited combination of prior art reference. Instead, Starling actually teaches away from the Examiner's suggested substitution

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of the microspheres of Crotts, which do not contain calcium phosphate, in the cell culturing system of Starling. For example, Starling teaches at col. 11, lines 7-13, that to produce their carriers, aforementioned technologies for fabricating porous ceramic hollow microspheres must be combined with either commercial sources of calcium phosphate materials or be allied to the chemical formulation of hydroxylapatite and/or other calcium phosphate compounds such as tricalcium phosphate (tribasic calcium phosphate).

Motivation to substitute the polymeric hollow microspheres of Crotts into the aggregate of Starling is also not provided in the teachings of Crotts since these teachings are focused on use of biodegradable polymeric microspheres in controlled release of therapeutic agents, not in aggregates for cell culture.

Further, the cited combination provides no reasonable expectation of success that hollow polymeric microspheres can be bonded in the manner claimed to produce a three dimensional scaffold with a density equal to or less than water and a fully interconnected pore network which promotes cell attachment and retaining of cell phenotype upon in vitro culturing with cells in a rotating bioreactor.

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Firstly, teachings of Starling imply that calcium phosphate is required for cell attachment. Crofts is silent with respect to any teachings whatsoever regarding cell attachment to their polymeric microspheres.

Secondly, all teachings in Starling relating to bonding and/or sintering of their microspheres into aggregates are at temperatures of at least 1000°C. At col. 12, beginning at line 64, Starling teaches that sintering of the fabricated hollow microspheres is conducted in the temperature range of about 1100°C to 1350°C, for periods of time of about 0.1 to 6 hours to densify the outer wall of the microspheres to a sufficient level of impermeability to ensure the suspendability required in typical bioreactor application using aqueous media. Such high temperatures cannot be used with polymeric microspheres. Instead, in the present invention, bonding is achieved and hollowness of the polymeric microspheres is maintained at much lower temperatures of for example 60°C, just above the glass transition temperature of the polymer. See teachings at page 8, line 31 through page 9, line 8 and page 15, lines 6-10 of the instant application. Crofts is silent with respect to formation of aggregates of microspheres. Accordingly, it is unpredictable based upon teachings of Starling and Crofts that hollow polymeric

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microspheres upon sintering into aggregates at low temperature required to remain hollow will provide a useful scaffold in bioreactor applications promoting cell attachment and maintenance of cell phenotype.

In an earnest effort to advance the prosecution of this case, Applicants have amended claim 1 to be drawn to a scaffold for tissue engineering consisting of biocompatible, biodegradable polymer-based hollow microcarriers, thus making clear that the microspheres do not contain calcium phosphate as required by Starling. Further, claim 1 has been amended to state that the polymeric microspheres are bonded together by heating at several degrees above the glass transition temperature of the polymer into a three dimensional scaffold which exhibits cell attachment and retaining of cell phenotype upon in vitro culturing with cells in a rotating bioreactor.

Since the cited combination of reference provide neither the motivation to make the instant claimed invention nor any reasonable expectation of success with respect to the instant claimed invention, the cited combination of references cannot render obvious the instant claimed invention. See MPEP 2143.

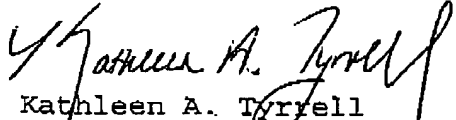
Withdrawal of this rejection under 35 U.S.C. 103(a) is therefore respectfully requested.

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Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,


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